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CHEMISTRY

Synthesis of Tetraazide Derivatives of *p-tert*-Butylcalix[4]arene Using Copper-Catalyzed Nucleophilic Aromatic Substitution

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Abstract—Aromatic azido derivatives of *p-tert*-butylcalix[4]arene have been obtained for the first time using copper-catalyzed nucleophilic aromatic substitution of azide anion for bromide in 5,11,17,23-tetrabromo-25,26,27,28-tetrabuthoxycalix[4]arene in a dioxane–water (3 : 1) solvent mixture with *N*,*N*-dimethylethylenediamine as a stabilizing ligand for copper(I). When the reaction is carried out under with microwave heating, partial substitution products (mono-, distally di-, proximally di-, and trisubstituted) can be isolated in satisfactory yields.

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Calixarene chemistry in recent decades has been one of the most successfully developed areas of macrocycle chemistry. Due to structural features, the calix[4]arene platform is widely used to design selective complexing agents, amphiphilic compounds, components of molecular devices, etc. [1, 2]. The introduction of azide groups into the calix[4]arene molecule provides a possibility to modify and introduce different functional groups [3] using click chemistry reactions: copper-catalyzed cycloaddition of azides to alkynes (CuAAC) [4].

Azide group is introduced most successfully into the lower rim of the macrocycle, which is widely used for aliphatic nucleophilic substitution of halogens [5]. Two approaches can be used to introduce azido groups into the upper rim of calix[4]arene. The first approach consists in the preliminary functionalization of the *para* position of calix[4]arene by the chloromethyl substituent followed by the nucleophilic substitution reaction with azides [6]. The second approach includes direct aromatic nucleophilic substitution of halogen by azide ion in tetrabromo derivatives of calix[4]arene. Such a substitution proceeds extremely slowly, however, the use of catalytic systems based on CuI in the presence of stabilizing ligands (proline, *N*,*N*-dimethylethylenediamine, etc.) showed their high efficiency by the example of bromo-containing phenols and alkoxybenzenes [7–9].

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The synthetic availability of the *para* position in tetrabromo calix[4]arene derivatives can provide the synthesis of the corresponding aromatic azido derivatives of the macrocycles. Therefore, the aim of this work is to prepare tetraazido derivatives of calix[4]arene with the aid of copper-catalyzed nucleophilic aromatic substitution.

Preliminary, we prepared tetrabromo-containing macrocycle **3** (Scheme 1). The synthesis included de-*tert*-butylation reaction of initial *p-tert*-butylcalix[4]arene [10] followed by alkylation of its lower rim [11] and bromination of the upper rim using the known procedures [12]. To perform the reactions of nucleophilic aromatic substitution based on the literature data, we selected solvent systems (Table 1) and ligands: L-proline (**L1**) and *N*,*N*-dimethylethylenediamine (**L2**). The reaction was conducted under both common heating and microwave heating.

The reaction course was monitored by thin layer chromatography (TLC). We found (Table 1, run nos. 1–3) that the reaction in the presence of **L1** did not occur or resulted in resinification both common heating and exposure to microwave radiation. The employment of **L2** as a ligand also proved to be inefficient. Thus, resinification of the reaction mixture took place in the majority of solvents (Table 1, runs nos. 4–9). Only a dioxane–water (3 : 1) mixture under heating for 55 h allowed isolation of target tetraazide **4** by column chromatography in 10% yield. The use of microwave radiation considerably accelerated the reaction to give 100% conversion after 3 h. Along with compound **4**, the reaction mixture contained also three products of partial substitution: compounds **5**, **6a** + **b**, and **7**, which were isolated by column chromatography. We